No new matter has been added.

Rejection of Claims Under 35 U.S.C. §112, first paragraph

Claims 1, 8, 10 and 26 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors, as the time the application was filed, had possession of the claimed invention.

The Examiner maintains his rejection asserting the application of the *Fiers*, *Amgen*, *Fiddes* and *Lilly* decisions. Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993); Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991); Fiddes v. Baird, 30 USPQ2d 1481, 1483 (Bd. Pat. Apps. & Int. Feb. 15, 1994); University of California v. Eli Lilly and Co., 43 USPQ 2d 1398 (Fed. Cir. 1997). Respectfully, Applicants disagree.

Applicants maintain that the facts of the present case and the facts under review in all of the foregoing cases cited by the Examiner are clearly distinguishable. Applicants direct the Examiner's attention to the explanation of the facts and interpretation of the decisions, as they relate to Applicants' invention, presented by Applicants in their previous response/amendment (Paper No. 14).

Further in support to Applicants' arguments, Applicants direct the Examiner's attention to the U.S.P.T.O.'s published "Synopsis of Application of Written Description Guidelines" (www.uspto.gov/web/menu/written.pdf), and in particular to Example 9, entitled "Hybridization," pp.35-37.

The hypothetical claim in Example 9 of the guidelines reads as follows:

> "An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO:1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity."

The analysis section following the hypothetical claim reads as follows:

> "A review of the full content of the specification indicates that the *essential feature of the claimed invention is the isolated nucleic acid that hybridizes to SEQ ID NO: 1 under highly stringent conditions and encodes a protein with a specific function.* The art indicates that hybridization techniques using a known DNA as a probe under highly stringent conditions were conventional in the art at the time of filing.
>
> *The claim is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO: 1 and must encode a protein with a specific activity.*

> The search of the prior art indicates that SEQ ID NO: 1 is novel and unobvious.
>
> There is a single species disclosed (a molecule consisting of SEQ ID NO: 1) that is within the scope of the claimed genus.
>
> There is actual reduction to practice of the disclosed species.
>
> Now turning to the genus analysis, a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs.
>
> *Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.*

The Example concludes that *"[t]he claimed invention is adequately described."*

In an analysis similar to the one provided in Example 9 of the guidelines, the specification of the present invention teaches that the essential feature of the claimed invention is the isolated nucleic acid that hybridizes to SEQ ID NO:1 under stringent conditions and encodes a protein (LEDGF) with a specific function (induction of protein synthesis in an epithelial cell).

The term "stringent conditions" is analogous to the term "highly stringent conditions" utilized in Example 9 of the guidelines. Example 9 defines "highly stringent conditions" as "6 x SSC and 65°C". Applicants' specification (see page 11, line 29 - page 12, line 3) and Claim 1 as amended herein, define "stringent conditions," as:

> "... hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrolidone, 0.02% Bovine Serum Albumin, 2.5mM $NaH_2PO_4$(pH7), 0.5% SDS, 2mM EDTA). SSC is 0.15M sodium chloride/0.15M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid.

Stringent conditions used in the hybridization of nucleic acids are well in the art and may be found in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York.

Thus, the art indicates that hybridization techniques using a known DNA as a probe under stringent conditions are conventional in the art at the time of filing.

Claim 1 of the present invention is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO: 1 and must encode a protein with a specific activity (i.e., induction of protein synthesis in an epithelial cell). Claim 1, as amended in Applicants' previous response (Paper No. 14), no longer contains language directed to "deletions, additions and substitutions of a nucleic acid molecule which hybridizes under stringent conditions to a molecule consisting of a nucleic acid of SEQ ID NO:1.

The search of the prior art indicates that SEQ ID NO: 1 is novel and non-obvious.

There is a single species disclosed (a molecule consisting of SEQ ID NO: 1) that is within the scope of the claimed genus.

There is actual reduction to practice of the disclosed species.

A person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the stringent hybridization conditions set forth in the claim yield structurally similar DNAs.

Thus, a representative number of species is disclosed, since stringent hybridization conditions (as described in the specification) in combination with the coding function of DNA (i.e., induction of protein synthesis in an epithelial cell) and the level of skill and knowledge in the art are adequate to determine that Applicants were in possession of the claimed invention. Therefore, Applicants' claimed invention is adequately described.

Claims 1, 8, 10 and 26 stand rejected under 35 U.S.C. §112, first paragraph. According to the Examiner "the specification, while being enabling for a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, does not reasonably provide enablement for nucleic acid molecules which hybridize to SEQ ID NO:1 and encode a lens epithelial cell derived growth factor polypeptide, or for a nucleic acid molecule comprising deletions, additions and substitutions of nucleic acid molecules which hybridize to SEQ ID NO:1 and encode a respective lens epithelial cell derived growth factor polypeptide, or for a fragment of SEQ ID NO:13 without regard to the structure and/or function thereof, or for an agent that binds a nucleic acid molecule."

Applicants direct Examiner's attention to the amendment of Claim 1 filed in Applicants' previous response (Paper No. 14). Claim 1 as amended no longer contains language directed to "a nucleic acid molecule comprising deletions, additions and substitutions of nucleic acid molecules which hybridize to SEQ ID NO:1.

Claim 1 as further amended herein is directed to: (a) nucleic acid molecules which hybridize under stringent conditions to a molecule consisting of the nucleic acid of SEQ ID NO:1 and which code for a polypeptide that induces protein synthesis in an epithelial cell (i.e., a specific function), wherein the stringent conditions are specifically defined, (b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and (c) complements of (a) or (b).

In view of the foregoing amendments and arguments, Applicants respectfully request withdrawal of the foregoing rejections of claims under 35 U.S.C. §112, first paragraph.

Rejection of Claims Under 35 U.S.C. §112 (second paragraph)

Claims 1, 8, 10 and 26 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the invention.

According to the Examiner, claims 1, 8, 10 and 26 are indefinite over the recitation of "stringent conditions because "stringency varies according to the hybridization conditions and the particular hybrid under study."

Claim 1 as amended herein recites that the stringent conditions comprise hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrolidone, 0.02% Bovine Serum Albumin, 2.5mM $NaH_2PO_4$(pH7), 0.5% SDS, 2mM EDTA), wherein SSC is 0.15M sodium chloride/0.15M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid.

Applicants believe that claim 1 as amended now conveys more precisely the metes and bounds of Applicants' invention, thus rendering the indefiniteness rejection moot.

According to the Examiner, claim 26 is indefinite over the recitation of "control" because "the claim does not set forth that material element or combination of elements which is unique to, and, therefore, definitive of a control."

Claim 26 as amended herein recites that the control comprises an amount of an isolated nucleic acid of the present invention (e.g., a nucleic acid of claims 1 or 4). Applicants are not changing the scope of the claim in so far as nucleic acid agents are concerned. This is not a limiting amendment in respect of nucleic acid agents as the scope of this term is not addressed by this amendment. Its original scope as filed is intended and Applicants expressly intend the full scope of equivalents that the law permits in

respecting this term. Applicants concede that the amendment is limiting in respect of polypeptide agents, and reserve the right to pursue this subject matter in continuing applications.

Applicants believe that claim 26 as amended now conveys more precisely the metes and bounds of Applicants' invention, thus rendering the indefiniteness rejection moot.

According to the Examiner, claims 4-7, 9, and 11 are indefinite over the recitation of "identifying a nucleic acid molecule encoding a LEDGF because the nature and the extent of the identification are not clear."

Claim 4 as amended herein no longer recites "a fragment of a nucleic acid molecule of SEQ ID NO:1 of sufficient length to represent a sequence identifying a nucleic acid encoding a polypeptide that induces protein synthesis in an epithelial cell," and is now directed to "a unique fragment of a nucleic acid molecule of SEQ ID NO:1 between 20 and 3360 nucleotides in length, and complements thereof.

A unique fragment of a nucleic acid molecule of SEQ ID NO:1, as claimed in amended claim 4 of the instant application, refers to a fragment of a nucleic acid molecule of SEQ ID NO:1 between 20 and 3360 nucleotides in length that acts as a signature for the larger LEDGF nucleic acid. As taught in the specification, unique fragments can be used as probes in Southern and Northern blot assays to identify such nucleic acids, or can be used in amplification assays such as those employing PCR. (see pages 13, line 13 – page 14, line 25). Those skilled in the art are well versed in methods for selecting such sequences, typically by performing homology searches using an algorithm such as NCBI's BLAST, although, in addition, they may also perform *in vitro* confirmatory hybridization and sequencing analysis.

Claim 4 as amended herein now conveys more precisely the metes and bounds of Applicants' invention, thus rendering the indefiniteness rejection moot.

Rejection of Claims Under 35 U.S.C. §112 (first and second paragraph) with regard the incorporation of GenBank References

Claims 4-7, 9, and 11, by incorporating GenBank sequences via their Accession Numbers, stand rejected under 35 U.S.C. §112, first and second paragraphs, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, and as being indefinite for failing to particularly point out and distinctly claim the invention.

Claim 4 as amended herein no longer refers to sequences via their GenBank Accession numbers. Claim 4 as amended herein now refers to sequences using each sequence's SEQ ID NO, thus rendering the foregoing 35 U.S.C. §112 (first and second paragraph) rejections moot.

Applicants believe that each of the pending claims is in condition for allowance. Applicants respectfully request that the Examiner telephone the undersigned attorney in the event that the claims are not found to be in condition for allowance.

If the Examiner has any questions and believes that a telephone conference with Applicants' attorney would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (Extension 232).

Respectfully submitted,

Edward R. Gates, Reg. No. 31,616
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, MA 02210
Tel. (617) 720-3500

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**X03/20/01**

## MARKED-UP CLAIMS

1. (Twice Amended) An isolated nucleic acid molecule selected from the group consisting of:

(a) a nucleic acid molecule which hybridizes under stringent conditions to a molecule consisting of the nucleic acid of SEQ ID NO:1 and which codes for a polypeptide that induces protein synthesis in an epithelial cell, wherein the stringent conditions comprise hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrolidone, 0.02% Bovine Serum Albumin, 2.5mM $NaH_2PO_4$(pH7), 0.5% SDS, 2mM EDTA), wherein SSC is 0.15M sodium chloride/0.15M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid,

(b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and

(c) complements of (a) or (b).

4. (Twice Amended) An isolated nucleic acid molecule selected from the group consisting of

(a) a unique fragment of a nucleic acid molecule of SEQ ID NO:1 between 20 and 3360 nucleotides in length [of sufficient length to represent a sequence identifying a nucleic acid encoding a polypeptide that induces protein synthesis in an epithelial cell], and

(b) complements of (a),

provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from the sequence group consisting of

(1) SEQ ID NO:14, 15, 16, or 21[sequences having the GenBank accession numbers of Table III],

(2) complements of (1), and

(3) fragments of (1) and (2).

26. (Twice Amended) A kit, comprising a package containing:

a nucleic acid [or polypeptide] agent that selectively binds to the isolated nucleic acid of claim 1, and

a control comprising an amount of an isolated nucleic acid of claim 1 or 4 for comparing to a measured value of binding of said nucleic acid [or polypeptide] agent to said isolated nucleic acid of claim 1.